THE REMARKS

The Amendments

The amendments in Claim 1 is supported by page 9, lines 1-3, and page 9, the first full paragraph.

The amendments in Claim 7 are supported by page 10, the 4th paragraph, and Claim 8.

New Claim 21 is supported by page 9, first full paragraph, and original Claim 1.

New Claim 22 is supported by page 10, 2nd paragraph.

New Claim 23 is supported by page 10, 3rd paragraph.

New Claim 24 is supported by page 10, 4th paragraph.

New Claim 25 is supported by Claim 13.

No new matter is introduced in any of the amendments. The Examiner is requested to enter the amendments.

The Response

35 U.S.C. § 112, Second Paragraph Rejection

Claims 1, 5, 7 and 8 are rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 8 is cancelled.

Claim 1 is amended to recite constant antibody domains.

Claim 7 is amended to recite according to the Kabat numbering system.

Therefore, the § 112, second paragraph rejection of Claims 1, 5, and 7 should be withdrawn.

35 U.S.C. § 112, First Paragraph Rejection

Claims 1, 2, 5-8, 13, and 18-20 are rejected under 35 U.S.C. 112, first paragraph as the specification allegedly does not provide enablement.

The non-enabling rejection relates to antibodies which bind to CD3 monovalently. Claim 1 has been amended to recite antibodies binding to TCR/CD3 complex bivalently or multivalently. Therefore, Claim 1 does not emcompass any monovalent binding antibodies.

Claim 7 is amended to recite that a cysteine at position H100A is changed to a serine.

In view of the claim amendments, the § 112, first paragraph rejection should be withdrawn

35 U.S.C. § 102(e) Rejection

Claims 1, 2, 13, 18-20 are rejected under 35 U.S.C. 102(e) as allegedly being anticipated by Digan et al. (US20020142000).

Digan et al. discloses a recombinant immunotoxin polypeptides comprising a CD3-binding domain and a Pseudomonas exotoxin mutant.

Claim 1 as amended recite a Fv antibody consisting essentially of at least two V_H and two V_L domains specific to CD3, which excludes exotoxin. Therefore, the amended claims are not anticipated by Digan et al.

35 U.S.C. § 103(a) Rejection1.

1. Claims 1, 2, 6, 13 and 18-20 are rejected under 35 U.S.C. 103(a), as allegedly being unpatentable over Smith et al. (WO9847531) in view of Hsu et al. (Transplantation. 1999 Aug 27;68(4):545-54), Holliger et al. (5,837,242) and Chapman et al. (Nat Biotechnol. 1999 Aug; 17(8):780-3).

The Instant Invention

The instant claims are directed to a bivalent, non-covalent dimeric anti-CD3 antibody of the so-called diabody format. This is illustrated by scFv6 diabody, which is a dimer and has a molecular weight of about 60kDa (see page 21, last three lines and page 22, , lines 1-2). scFv6 diabody consists of two Fv peptide chains and has a peptide linker of 6 amino acids between the V_H domains and the V_L domains. The short 6 amino acid linker of scFv6 does not allow a folding of the peptide chain, but forces the Fv peptide chain to associate with another Fv peptide chain to form a dimeric and bivalent diabody.

It is shown in the application that scFv6 diabody has a much greater immunosuppressive effect as measured by CD3 downregulation and inhibition of T cell proliferation in a mixed lymphocyte reaction (MLR) than the original parental OKT3 antibody, and in contrast to the

parental OKT3, scFv6 diabody caused no significant release of cytokines; see Example 6, page 25 and Fig. 9. Further, the bivalent binding of the scFv6 diabody to CD3 on a cell surface is demonstrated in Example 3, page 23, 1st full paragraph; the respective data is shown in Table 1 on page 24.

Smith et al.

Smith et al. dislcose $F(ab')_2$, which have a distinct structure from that of the diabody of the present invention. $F(ab')_2$ are coupled by a hinge-joint which gives flexibility to the antigen binding domains to orientate towards the respective epitopes on CD3 molecules. Although Smith et al. teach that $F(ab')_2$, which are a large portion of a whole antibody, can be immunosuppressant, this would not have made obvious that synthetic diabodies having a different and rigid structure compared to $F(ab')_2$ may be an immunosuppressant in the same way.

Considering the different and rigid structure of the synthetic bivalent diabody, a person of ordinary skill in the art would not have expected that such a rigid antibody is capable to bivalently bind to CD3 molecules exposed on the cell surface such that the diabody exhibits a much greater immunosuppressive effect as measured by CD3 downregulation and inhibition of T cell proliferation in a mixed lymphocyte reaction than the parental antibody.

Although Smith et al. teach that $F(ab')_2$ were inappropriate for clinical use due to small available quantities, reduced serum half-life and contamination with whole mAb, Smith et al. do not indicate that the drawbacks of $F(ab')_2$ are related with the constant CL and CH1 domains of Fab-fragments. Smith et al. disclose that the side-effects are a consequence of the cross-linking through the Fc portion of the anti-CD3 antibody and these side-effects can be avoided by Fc receptor non-binding anti-CD3 antibodies. Smith et al. do not provide any motivation to replace a $F(ab')_2$ by the claimed diabody. In particular, Smith et al. do not provide any suggestion to make a diabody devoid of constant domains:

Hsu et al.

Hsu et al. report that a Fc receptor non-binding anti-CD3 antibody is not associated with serious side-effects. Hsu et al. report that a significant cytokine release occurs when the Fc domain of a human anti-CD3 antibody is able to bind to Fc receptors on chimpanzee cells. Hsu et

al. do not suggest making an antibody devoid of constant domains including CL and CH1 domains.

Holliger et al.

The instant claims are not obvious over Holliger et al., because Holliger et al. teach to use bivalent diabodies for cross-linking CD3 to activate T cells (col. 22, lines 15-16). Further, Holliger et al. teach "unprimed T-cells can be activated through bridging of two CD3 molecules on the T-cell surface" (col. 26, lines 22 and 23). Therefore, Holliger et al. teach away from the claimed diabodies that suppress immune reaction.

Chapman et al.

Chapman et al. disclose antibodies. Chapman et al. do not teach or suggest diabody.

In summary, Smith et al. and Hsu et al. disclose making Fc receptor non-binding anti-CD3 antibodies of a whole antibody or fragments thereof, i.e. $F(ab')_2$. However, Smith et al. and Hsu et al. do not teach or suggest the claimed bivalent and non-covalent dimeric diabody. A person of ordinary skill in the art would not have been motivated with a reasonable expectation of success to make an immunosuppressant anti-CD3 diabody as claimed, because Holliger et al. teach that diabodies cross-linking the CD3 antigen on the same surface would activate T-cells (col. 22, lines 12-16) and not suppress them.

Therefore, the 103(a) rejection of Claims 1, 2, 6, 13 and 18-20 over Smith et al., in view of Hsu et al., Holliger et al. (5,837,242), and Chapman et al. should be withdrawn.

2. Claims 1 and 5-8 are rejected under 35 U.S.C. 103(a), as allegedly being unpatentable over Smith et al., in view of Hsu et al., Holliger et al., and Chapman et al. as applied to claims 1, 2, 6, 13 and 18-20 above, and further in view of Kipriyanov et al. (Protein Eng. 1997 Apr; 10(4):445-53).

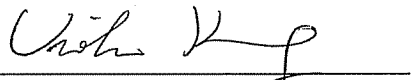
Kipriyanov et al. do not disclose or suggest that an OKT3 scFv shows an immunosuppressive effect. Therefore, the addition of Kipriyanov et al. does not cure the deficiency of other cited references.

CONCLUSION

Applicants believe that the application is now in good and proper condition for allowance. Early notification of allowance is earnestly solicited.

Date: March 27, 2009

Respectfully submitted,



Viola T. Kung, Ph.D. (Reg. No. 41,131)

HOWREY LLP
2941 Fairview Park Drive, Box 7
Falls Church, VA 22042
Tel: (650) 798-3570
Fax: (650) 798-3600